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BORDEN'S REVIEW

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PANTOTHENIC ACID:

ITS NUTRITIONAL SIGNIFICANCE

BORDEN'S REVIEW
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PANTOTHENIC ACID:*
ITS NUTRITIONAL SIGNIFICANCE

Although the earliest recognition of the biological significance of pantothenic acid was in its role as a growth stimulant or "nutrilite" for yeast, the fact that it would eventually prove to be a vitamin required by animals was considered likely from the time of its discovery in a bios concentrate in 1931 (1). Two years later, when a complete report on the new growth substance appeared (2), its possible relationship to what was then known as "vitamin G" (i.e., the vitamin B_2 complex) was discussed. It was practically impossible, in the early studies on pantothenic acid, to demonstrate its vitamin nature. This was due to the fact that a suitable synthetic diet, lacking only pantothenic acid, could not be devised at a time when many of the other B vitamins were still unknown or unavailable in pure form.

With the advances in poultry science leading to the postulation of an "anti-dermatitis (filtrate) factor" for chicks, the way was cleared. Chemical studies of the unidentified "filtrate factor" proceeded simultaneously with attempts to isolate and identify pantothenic acid. Investigators in poultry nutrition and chemists studying pantothenic acid soon suspected that their studies might converge to reveal a mutually common biological factor. This proved indeed to be the case, for closely following the announcement of the structure and synthesis of pantothenic acid (3) the poultry nutritionists (4, 5) recognized and announced its identity with their "filtrate factor".

Following this, studies were made with chicks using pure pantothenic acid in place of the filtrate factor, thereby confirming the significance of pantothenic acid as a vitamin for chicks. Later work showed that the newly recognized vitamin is essential for rats, dogs, pigs and other animals, as well as for man. The original "anti-dermatitis" activity of pantothenic acid has now been extended to include a considerable number of additional functions.

Pantothenic Acid in Animal Nutrition:

Chicks: Almost simultaneously with the initial work of Williams and coworkers in separating pantothenic acid from "bios", the first description of an experimentally produced nutritional dermatitis in chickens was published by Ringrose, Norris and Heuser (6) in 1931. The dermatitis was marked by the formation of a granular, viscous exudate about the margins of the eyelids, crusty scabs at the corners of the mouth, and thickening, cornification, cracking and fissuring of the skin on the bottoms of the feet and between the toes.

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* The first section of this paper appeared in the February 1944 issue of *Borden's Review of Nutrition Research.*

A year later, Kline *et al* (7) devised a special "heated diet" which consistently produced the dermatitis. The effectiveness of the heated diet in producing the characteristic symptoms was reported by Elvehjem *et al* (8) to be due to lack of a liver "filtrate factor". Subsequent work indicated that the heated diet was deficient in more than one B vitamin (9). Following modifications of the diet to include the known missing factors, the cause of the dermatitis was traced by Bauernfeind and Norris (10) to a new growth factor which was shown to be adsorbed on fuller's earth. As has already been described, this factor was eventually identified with pantothenic acid, although it is believed by some that pantothenic acid accounts for only a part of the activity of the liver "filtrate factor" (11, 12).

Additional studies have shown that pantothenic acid deficiency in the chicken is not limited to dermatitis. Mature laying hens kept on a heated diet free from pantothenic acid for 28 weeks failed to develop any outward evidence of pantothenic deficiency with respect to dermatitis, egg production or mortality (13). This was taken as evidence of pantothenic acid storage in the tissues of adult fowl. The hatchability of the eggs, however, dropped from over 60% to less than 3%. Those chicks, which did hatch, showed very early symptoms of dermatitis. In addition to almost complete loss of hatchability, it was found that reproduction on a pantothenic acid-free diet is impossible.

Other investigators, studying pantothenic acid deficiency in the chick, reported the occurrence of extensive spinal cord lesions curable only by pantothenic acid (14). Associated with these lesions, they found keratitis and dermatitis, involution of the thymus and fatty livers. An adequate supply of pantothenic acid has also been found necessary for optimal growth in the chicken.

On the basis of extensive studies, the pantothenic acid requirement of chicks has been set by Jukes (15) at about 1.4 mg. per 100 grams of feed.

Rats: Following the establishment of pantothenic acid as an animal vitamin factor, based on experimental evidence with chicks, interest was focused upon other possible functions of this vitamin. A series of studies was conducted, therefore, with the conventional experimental animal, the laboratory rat. Not only dermatitis and impairment of growth have been reported as a result of pantothenic acid deficiency in the rat, but also adrenal damage (16, 17, 18, 19, 20), disturbance of hair growth, accompanied by graying or rusting of the hair and the appearance of "blood-caked" whiskers (21).

Pantothenic acid deficiency damages the adrenal cortex seriously, and many of the symptoms associated with the deficiency are due to loss of function of the adrenal cortex. Prominent among the functions of the cortex is the regulation of salt and of water balance. In this connection it has been noted that a low salt diet enhances the graying of hair due to pantothenic acid deficiency (22), and that pantothenic acid deficiency increases the desire of rats for salt (20). The phenomenon of "blood-caked" whiskers which has been found to be due not to blood, but to the deposition of a red pigment excreted by the tear glands (23), is associated with dehydration and cannot be cured by any combination of vitamins as long as dehydration persists.

The pantothenic acid requirement of the rat has been set at about 80 micrograms per day (21).

Dogs: The importance of pantothenic acid in the nutrition of dogs has been indicated by many workers. In 1942, a very complete discussion of the subject was published by Schaefer *et al* (24). One of the most striking effects of the deficiency is the suddenness with which the animals on a pantothenic acid deficient diet fail. No symptoms may be evident and eating may continue normally for some time until sudden prostration or coma occurs. Coincident with this condition, gastrointestinal and respiratory disorders as well as convulsions have been noted. Prompt treatment with pantothenic acid, over a prolonged period of time, succeeded in many cases in restoring the animals to normal. In some cases, however, the damage was found to be irreparable and death ensued. Post-mortem examinations have revealed evidence of hemorrhagic kidneys and fatty liver.

The pantothenic acid requirement of the dog is estimated to be about 100 micrograms of calcium pantothenate per kilo (2.2 lbs.) of body weight per day for young puppies, and somewhat less for adult dogs.

Pigs: Chick, Hughes, Wintrobe and their respective colleagues (25, 26, 27) have reported on the importance of pantothenic acid in the nutrition of pigs. Symptoms similar to those seen in the chick and dog have been noted as a result of pantothenic acid deprivation. In addition, sensory neuron degeneration (28) and consequent locomotor incoordination (29) have been reported. Pantothenic acid and, in some cases, pyridoxine have been used to successfully treat these conditions. Other characteristic symptoms include diarrhea, followed by dysentery, loss of appetite, marked impairment of growth, loss of hair, and inflammation and ulceration of the intestinal tract.

The requirement of the growing pig is believed to be approximately 7.8 to 11.8 milligrams per 100 lbs. of body weight per day.

Other Animals: The role of pantothenic acid in the nutrition of animals, including cattle, sheep and others, as well as the species discussed in the present Review, has been summarized in a comprehensive review by Williams (30).

Pantothenic Acid and Nutritional Achromotrichia:

An apparent relationship is believed to exist between nutritional factors and the loss of color (achromotrichia) or graying of hair. A great deal of evidence for and against the existence of such a relationship has accumulated in recent years, but up to the present time, the question has not been satisfactorily resolved. The current consensus is that graying of the hair in man and other animals may be caused by a wide variety of factors one group of which may very well be of nutritional origin. Gray hair resulting from nutritional deficiencies has, in a very few instances, been restored to normal color by dietary means. Gray hair, resulting from causes other than improper nutrition, does not respond to any kind of vitamin therapy. Beyond these empiric facts, little is known concerning any actual dietary factor or factors which may be effective chromotrichia agents.

Evidence has been presented, at one time or another, to indicate that pantothenic acid, para-aminobenzoic acid, folic acid and even biotin may function as "anti-gray hair factors" in experimental animals (31, 32, 33, 34, 35), but in many of these cases evidence to the contrary has also been forthcoming. It is beyond the scope of this Review to discuss the entire aspect of nutritional achromotrichia and the postulated significance of the various vitamin factors said to be involved. The present Review is necessarily limited to a discussion of the existing evidence concerning the role of pantothenic acid as a chromotrichial factor.

About six years ago, Morgan and her associates (36) reported graying of the fur in black rats which had been kept, for experimental study, on diets deficient in the vitamin B complex. They found that normal hair color could be restored by addition of the "filtrate factor" to the diet. Two years later, Morgan and Simms (37) found that lack of the same filtrate factor in the diet of the silver fox leads to the development of an inferior grade of fur with an excessive degree of "silvering". Brewers' yeast and liver were shown by other investigators to be equally effective in restoring normal hair color of rats maintained on deficient diets.

With the subsequent identification of pantothenic acid as the filtrate factor (or, at least, as a major constituent thereof), this vitamin, in the form of its calcium salt, was tested for its anti-graying value. György and Poling (31), Unna and Sampson (32) and a number of others reported calcium pantothenate effective for both the prevention and cure of graying fur in animals maintained on pantothenic acid-free diets. In conflict with these reports, R. R. Williams (38) indicated the complete ineffectiveness of pantothenic acid as an anti-gray hair factor. These controversial findings may be attributed, at least in part it is believed, to differences in the basal diets used by the various workers. Unna and associates (39) have firmly upheld the anti-gray hair function of pantothenic acid in rats, pointing out that comparable quantities of dried liver or rice bran were no more effective than pure pantothenic acid in restoring normal fur color.

Human Studies: The value of pantothenic acid, in combination with para-aminobenzoic acid, as an anti-gray hair factor for man was reported about four years ago (40) and, although subsequently unconfirmed by other workers, achieved a great deal of publicity in the popular press. Less than a year ago, another series of experiments with men and women was reported by Brandaleone *et al* (41), in which calcium pantothenate, para-aminobenzoic acid and brewers' yeast were administered over a long period of time and under carefully controlled objective conditions.

In this experiment, nineteen elderly men and women with white or graying hair were selected as volunteer subjects from the wards of the Goldwater Memorial Hospital in New York City, where they were confined with chronic disturbances including rheumatoid arthritis and general arteriosclerosis. The patients were divided into three groups and received the following dietary supplements daily for a period of eight months:

Group 1.	7 patients	100 mg. calcium pantothenate 200 mg. para-aminobenzoic acid 50 g. brewers' yeast
Group 2.	5 patients	para-aminobenzoic acid brewers' yeast
Group 3.	7 patients	calcium pantothenate brewers' yeast

Photographs, hair clippings and clinical observations were made at regular, frequent intervals during the course of the experiment. Several changes were noted and described as follows:

"The most common (change) was the appearance of a yellow or greenish cast to the gray hair, most often observed during the first few months, which did not always persist. Secondly, growth of scattered wiry black hairs became apparent. In several patients there was thought to be greater luster without actual change in color. In one man whose hair was sparse, there was an increase in the number of hairs. In only two patients was there unequivocal change of color. Both . . . suffered from rheumatoid arthritis. Both were men . . . had brown hair—the one a red-brown, the other a yellow-brown. The change in color . . . tended toward a return to the original color. Both men noticed the change themselves. It became apparent after the drugs had been administered for . . . two or three months, thereafter increasing slowly in intensity until the drugs were stopped."

Thus, in only two individuals out of nineteen was an unequivocal change in color noted. These two were members of the group receiving all three supplements. For this reason, no conclusion can be drawn as to the actual identity of the anti-gray hair factor (or factors). However, the experiment does provide some evidence to indicate that, in certain persons, gray hair may be changed significantly toward its original color by nutritional means.

Pantothenic Acid in Human Nutrition:

Following the establishment of pantothenic acid as an essential vitamin for various species of animals, scientific interest was naturally focused upon the possible significance of this factor in human nutrition. Clinical studies along these lines have only recently begun.

The first report of a clinical trial indicating that pantothenic acid has a probable function in human nutrition was that of Spies and coworkers (42) in 1940. They found that the concentration of pantothenic acid in the blood of malnourished persons (patients suffering from pellagra, beriberi and riboflavin deficiency) was from 23 to 50 percent lower than that of normal individuals. They found further that injection of pantothenic acid in either normal or malnourished subjects produces a temporary rise in the pantothenic acid level of the blood as well as a 20 to 30 percent rise in the blood riboflavin level. Likewise, injections of riboflavin were found to be accompanied by increases in the blood levels of both of these vitamins. From these results they conclude that pantothenic acid is necessary to human beings and that its function is in some way closely associated with that of riboflavin. This latter conclusion is of particular interest in connection with the recent findings of Supplee (43) discussed in the first section of this Review.

Additional available evidence concerning the possible function of pantothenic acid in human beings has recently been reviewed by

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Gordon (44). "From the available evidence in animals," he states, "lesions due to pantothenic acid deficiency in the human may occur in the nervous or endocrine systems or they may involve the skin or hair." In this connection several interesting cases are cited. According to the report, five cases of peripheral neuritis, and one case of acute psychosis in a male alcoholic with severe peripheral neuritis all responded promptly to pantothenic acid therapy after failure to improve when other B vitamins were administered. The possibility exists that the responses may not have been due entirely to the pantothenic acid, but, in some cases, to a probable delayed effect of the other B vitamins as well.

On the basis of animal experiments, Gordon has indicated the possibility that certain types of human adrenal insufficiency such as non-tuberculous Addison's disease may be the result of nutritional deficiency, particularly pantothenic acid deficiency. The probable role of pantothenic acid in maintaining the integrity of the nervous system is discussed and it is suggested that pantothenic acid may prove to be one of the missing factors in the multiple deficiency disease known as "nutritional neuropathy." Gordon concludes:

> "While many of the clinical observations presented above can hardly stand up under close scrutiny, they may, nevertheless, serve as a step toward more carefully controlled studies in the future. They are of sufficient interest to warrant the extension of careful quantitative clinical investigations of nutritional deficiency disease to include pantothenic acid. For the results of animal experimentation have already pointed to a number of leads, the further study of which must be accepted by investigators in the clinical field."

Human Requirement for Pantothenic Acid: Although pantothenic acid is widely distributed in nature, the amounts occurring in various foods vary greatly, so that the possibility of pantothenic acid deficiency in man is not remote, especially in conjunction with other B-complex deficiencies.

From a comparison of riboflavin requirement values derived from excretion studies, with pantothenic acid excretion studies, Gordon (44) has suggested a speculative pantothenic acid requirement of 9 to 11 mg. per day for adults. Similar values were arrived at independently by Williams (45) using a different basis for calculation. On the assumption that an average dietary intake providing 2500 calories per day should also provide approximately the correct vitamin requirement, he calculated the amount of pantothenic acid, which would be supplied by 2500 calories of foods of high nutritive value such as cow's milk, liver or eggs. He found that 2500 calories of such foods invariably provide 10 to 12 mg. of pantothenic acid. From

this it was deduced that 10 to 12 mg. of pantothenic acid per day (or per 2500 calories of food) is probably an adequate level for adults, with correspondingly larger levels for children.

Sources of Pantothenic Acid: The development of assay methods for pantothenic acid has made possible an analysis of various common foods and animal feeds for pantothenic acid content.

Three general methods are in use for making pantothenic acid determinations. They involve measuring the growth response of yeast cells, chicks and of lactic acid bacteria. These methods, their applications and relative merits, are discussed in a review by Williams (30).

The pantothenic acid content of a wide variety of products has been given by many workers. The following table, condensed from a list compiled by Jukes (46) gives typical values for various representative products.

Distribution of pantothenic acid in certain products of natural origin, in terms of micrograms of pantothenic acid per gram of edible material.

MATERIAL	PANTOTHENIC ACID CONTENT IN MICROGRAMS PER GRAM				NUMBER OF ASSAYS
	Dry material		Undried basis		
	Range	Average	Range	Average	
Excellent sources (more than 28 micrograms per gram of dry material)					
Brewers' dried yeast	140 to 350	200			10
Liver, mammalian	100 to 270	180	25 to 60	40	4
Egg yolk	100 to 200	125	50 to 100	63	4
Eggs	32 to 190	108	8 to 48	27	37
Commercial "liver meal"			100 to 110	105	2
Broccoli leaves and blossoms		87		14	1
Cane molasses, "black strap"	5 to 100	70			11
Peanut meal			45 to 63	53	3
Whey	36 to 85	60	2.4 to 5.7	4	17
Broccoli		46		11	1
Buttermilk, churned	35 to 56	46	3.5 to 5.6	4.6	4
Sweet potatoes	31 to 46	38	10 to 12	11	2
Lean beef		38		10	1
Skim milk	21 to 43	36	2.1 to 4.3	3.6	9
Zucchini squash		35		3	1
Kale	23 to 36	30	2.3 to 3.6	3	2
Good sources (14 to 28 micrograms per gram of dry material)					
Canned salmon		28		7	2
Irish potatoes		28		6.5	2
Alfalfa	3 to 40	25			12
Wheat bran			20 to 30	24	4
Canned pumpkin		23		4	1
Whole milk	10 to 32	22	1.3 to 4.2	2.8	4
Split peas			20 to 22	21	2
Tomatoes		20		1	2
Cowpeas			17 to 20	18	2
Soybean meal			8 to 22	14	4

According to the table, liver, eggs, green vegetables such as broccoli, kale and zucchini squash, buttermilk and skim milk are some common foods which are excellent sources of pantothenic acid on a per gram basis. Brewers' yeast, molasses, peanut meal and whey are also exceptionally rich in the vitamin. On the same basis, among the common components of the average diet, whole milk, potatoes, wheat bran and canned salmon rank as good sources of pantothenic acid. Considering the pantothenic acid values of these foods on the basis of the quantities and regularities in which they are consumed in the average diet, it becomes apparent that certain of the common foods listed as good sources such as whole milk, potatoes or tomatoes, become in reality especially significant dietary sources of pantothenic acid.

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NEWS DIGEST

PRENATAL DIET – A statistically significant relationship has been shown between the diet of mothers during pregnancy and the condition of the offspring at birth and during the first two weeks of life. On the basis of more than 200 case histories, it is predictable that a poor prenatal diet will result in the birth of an infant whose physical condition is poor. In the study reported, all stillborn infants, all premature and functionally immature infants, all infants who died soon after birth (except one) and most infants with marked congenital defects, were born to mothers whose diets during pregnancy were very inadequate. Mothers whose prenatal diets are good or excellent may be expected to have infants who are in good or excellent physical condition, although rare exceptions may occur (one case out of 216 in the study reported). *J. Nutr. 26,* 569 (1943).

THIAMIN IN PORK—A new experimental method has been devised for reducing the loss of thiamin in dehydrated pork during storage at the high temperatures of warehouses or docks. The method involves adding to the dehydrated pork a cereal-milk-bone mixture which apparently exerts a stabilizing effect on the vitamin. The discovery was made during storage studies of a food for animal pets. The ingredients of the pet food were meat and meat by-products, tomato paste and approximately 33% of a mixture of cereals, milk and bone meal. When cooked and dehydrated, this pet food retained most of its thiamin for several weeks at 120° F., a temperature known to cause severe destruction of thiamin in dehydrated meats. Since the cereal-bone-milk mixture retained thiamin at high temperatures, it was reasoned that it might stabilize the thiamin content of the dehydrated meat to which it was added. Tests showed this to be so, and it is believed that the vitamin values of certain other foods also may be preserved by this method. *Science 98,* 449 (1943).

SOYBEANS—To strengthen wartime diets nutritionally, more than twelve times the quantity of soybean products available last year has been allocated to civilians for the year ending June 30, 1944. Although most of the supply is to be used for war purposes overseas, particularly for meeting critical nutrition needs of liberated nations, the expansion will permit civilians in the United States to use large quantities of high-protein soybean products. Out of every 100 lbs. of soybean flour, flakes and grits products, 27 lbs. have been allocated for civilian consumption. This represents a total of 362,500,000 lbs. as compared with a domestic use of only 30,000,000 lbs. last year. *Chem. Eng. News, Oct. 10,* (1943).

DENTAL CARIES—Bone flour, containing significant amounts of calcium, phosphorus and fluorine*, has been suggested as a possible prophylactic and therapeutic aid in the control of dental caries. A recent report describes clinical tests on nine patients with high caries incidence each of whom was given a capsule containing 5 grams of bone flour three times daily. No other dietary changes were made. Treatment was extended over a nine-month period. During this time the patients were examined monthly and the incidence of new caries or changes in the development of existing caries were noted. Only one new cavity was discovered and existing cavities showed no further extension. *J. Amer. Dent. Assoc. 30,* 1396 (1943).

*[See *Borden's Review of Nutrition Research* on Fluorine and Dental Health, Vol. 3, No. 3 (1942)].

THIAMIN AND BAKING – Appreciable destruction of thiamin occurs in the preparation of many cakes, biscuits, crackers, and other hard-baked foods, due to the use of baking powder and heat and to the relatively large surface area of individual pieces. Baking powder increases the alkalinity of the batter, a condition which favors thiamin destruction, as does heating at high temperatures. Large surface areas mean greater exposure to oxidative processes. These problems must be considered in the planning of enriched flours for this type of baked goods. *Food Fld. Rptr. p. 25, Nov. 1* (1943).

SEA WATER IN BREAD–The Quartermaster Corps has recently developed a formula for bread in which sea water is used to replace fresh water in certain war areas where fresh water may be limited. The salt water is strained through cloth to remove foreign particles and then treated with calcium hypochlorite in the same manner as is fresh water of doubtful purity for drinking purposes. Instead of using 60 parts fresh water and 2 parts of salt, 62 parts of salt water are used. Other ingredients remain the sa Finished bread made in this mann showed only a slight variation fr bread made according to the standa recipe. *Baker's Review, Feb.* (1944).

VITAMIN C IN POTATOES – Po toes, if properly prepared and eat daily, can rank with citrus fruits, su as oranges and lemons, as an import source of vitamin C. In view of t plentiful potato crop predicted for 19 government nutrition authorities ur greater use of this valuable food to e hance the nutritive value of present w time diets. It is estimated that the regul use of potatoes in the diet may provi as much as 25% of the average adu vitamin C requirement, in addition significant amounts of B vitamins, ir and other minerals. Potatoes also pr vide good quality protein for tiss building and repair, and starch for fue Controlled cookery tests have indicat that the nutritive values are best r tained when potatoes are steamed, boil or baked in their jackets. *Consume Guide, Feb.,* (1944); *Sci. Digest, Ma* (1944).